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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/542,043	CANTOR ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) ____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-23 are pending and examined on the merits.
Claim 24 is cancelled.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/17/2008 has been entered.

This Office Action is in reply to Applicants' correspondence of 12/17/2008.
Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.
This Action is **NON-FINAL**.

Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Claim Objections

1. Claim 7 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 7 recites the limitation that 'genotyping is performed using primer extension and mass spectrometric detection', however claim 7 depends from claim 1, where the independent claim requires 'using primer extension and MALDI-TOF mass spectrometric detection' to

genotype the sample. As such the limitations of claim 7 do not further limit the requirements of the base claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claims 2, 10, 12, and 18 are objected to over the recitations of 'steps a-c' (claims 2 and 10), 'steps b-d' (claim 13), and 'steps b-f' (claim 18); where the phrases 'steps (a), (b), and (c)', 'steps (b), (c), and (d)' and 'steps (b), (c), (d), (e), and (f)' are more appropriately consistent with the independent claims from which the objected to claims depend.

Withdrawn Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

2. The rejections of claims under 35 U.S.C. 112, second paragraph, as being indefinite, as set forth on pages 3-4 of the Office Action of 07/23/2008 are **WITHDRAWN** as set forth in the Advisory Action of 11/20/2008.

Maintained Claim Rejections - 35 USC § 103
As necessitated by the amendments to the claims

3. Claims 1, 2, 4-8, and 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruano et al (1990) in view of Furlong et al (1993) and Ross et al (citation no. 27 on the IDS of 07/31/2006).

Ruano et al teaches a method for the analysis of haplotypes amplified from a single DNA molecule.

Regarding claim 1, Ruano et al teaches that a nucleic acid sample from a subject is diluted to form a solution containing a single copy of the target molecule (p.6297 – Dilutions; Fig 3), relevant to step (a). Relevant to step (b), the reference teaches the amplification of target DNA using two primer pairs (GR1, GR3 and GR2, GR4) that amplify a region comprising 3 polymorphic sites (i.e.: primers GR1 and GR3 type a TG deletion; primers GR2 and GR4 type two separate SNPs) (Fig 1; p.6297 – Target for amplification). Further relevant to step (b), the reference teaches that distant segments of an intact template molecule can be analyzed by PCR with multiple primer pairs for direct haplotype determination (p.6300 – Discussion). Relevant to step (c), Ruano et al teaches the genotyping of sites amplified from the single molecule dilution target DNA by southern hybridization (Fig 4) and restriction digestion (Fig 3). Relevant to step (d), the reference teaches that information regarding the individual genotypes is combined to determine the haplotype of the subject (Fig 4; p.6298 – Typing and direct haplotype determination of SMP products).

Regarding claim 2, Ruano et al teaches that additional experiments are performed on sample DNA to resolve constituent haplotypes of heterozygous individuals (p.6298, right col., last paragraph; Fig. 3; Fig 4), and that each experiment followed the scheme present in Figure 3 of the reference, thus comprising steps (a)-(c) as recited in claim 1. The reference specifically teaches that for 'Person B' the experiment was repeated five times, and that four haplotypes (each comprising the component genotypes) were resolved (Fig 4; p.6299 – Individual B). The comparison of

multiple deduced haplotypes to determine the haplotype of the subject is a statistical analysis.

Regarding claims 4-6, Ruano et al teaches the analysis of a haplotype comprising polymorphic sites that are single nucleotide polymorphisms and a dinucleotide insertion/deletion (Fig 1).

Ruano et al does not specifically teach the analysis of at least three polymorphic markers that are about one or more kilo base pairs apart (as recited in the preamble of claim 1), or the amplification of a single molecule dilution with at least three primer pairs that each amplify a different nucleic acid region that comprises at least one polymorphic site (step (b) of claim 1). Ruano et al does not exemplify producing 12-18 replica genotypes (claim 8), polymorphic markers that are three or more, or four or more kilo base pairs apart (claims 21 and 22), or flanked regions that are about 100 bp long (claim 24). However such methods where well known in the art at the time the invention was made.

Furlong et al teaches the haplotype analysis of flow sorted single sperm cells (p.1192 – Flow sorting single sperm), which contain a single molecule dilution of each human chromosome. Relevant to the required limitations of the rejected claims, Furlong et al teaches amplifying nucleic acid from a single sperm cell with at least three primer pairs (p.1192 – PCR primers) that each amplify a different nucleic acid region that comprises at least one polymorphic site (step (b) of claim 1); and teaches the amplification of the polymorphic loci D9S109, D9S127, and D9S53, which are polymorphic loci that are about one or more kilo base pairs apart (claim 1) and three or

more kilo base pairs apart (claim 21) and four or more kilo base pairs apart (claim 22). Relevant to the requirements of step (b) of claim 1, Furlong et al teaches the amplification of a single sperm cell nucleic acids with at least three primer pairs that each amplify a different nucleic acid region that comprises at least one polymorphic site (p.1192 – PCR of single sperm). Regarding the limitations of step (b) of claim 1, it is noted that Furlong et al teaches amplification using primers that flank a nucleic acid region of about 100 base pairs.

Neither Ruano et al nor Furlong et al specifically teach the analysis of amplified polymorphic genotype markers using primer extension and mass spectrometric detection, as required by step (c) of claim 1 and claim 7. However the genotyping of amplified nucleic acid molecules using primer extension and mass spectrometric detection was well known in the art at the time the invention was made.

Ross et al teaches methods of multiplex genotyping using primer extension and mass spectrometry (p.1347, right col., lns.3-11). The reference teaches a method comprising the steps of amplification of 12 polymorphic loci and subsequent primer extension using oligonucleotide primers and ddNTPS (p.1350 – Experimental protocol, PCR). The reference further teaches analysis of the primer extension products by MALDI-TOF mass spectrometry (p.1350 – Experimental protocol, MS; Fig.2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have performed the haplotype of the analysis of the polymorphic markers as taught by Furlong et al, including amplification using at least three primer pairs, incorporating the single molecule dilution and genotype analysis of

Ruano et al. One would have been motivated to analyze the markers as taught by Furlong et al based on the teachings of Furlong et al that the markers may be associated with epithelioma (p.1191, right col.). One would have been motivated to use the multiple pairs of primer based on the teachings of Ruano et al that distant segments in a molecule are amenable to PCR with multiple primer pairs for direct haplotyping (p.6300, left col., Discussion).

Regarding claim 8, Ruano et al teaches repetition of experimentation to resolve genotypes (p.6298 – right col., last paragraph), and further teaches that errors in haplotype determination should be held in check by analyzing replicate vials (p.6300, left col., lns.43-45). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the haplotype determination methods of Ruano et al to produce and analyze 12-18 replicas. One would have been motivated to create multiple genotype replicas based on the assertion of Ruano et al that such methods increase the accuracy of the analysis (p.6298 – right col., last paragraph; p.6300, left col., lns.43-45). One of skill in the art would recognize that creating an increased number of replica genotypes would lead to further increased accuracy of haplotype determination, and the skilled artisan would be capable of creating, for example, 12 genotype analyses of single-molecule dilutions (e.g. Ruano et al teaches twelve total analyses in Fig 4).

Further, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the haplotype analysis methods of Ruano et al in view of Furlong et al so as to have incorporated the primer

extension/mass spectrometry based genotype detection methods of Ross et al, as required by step (c) of claim 1 and claim 7. One would have been motivated to use the methods of Ross et al based on the teachings of Ross et al that primer extension/mass spectrometry based methods eliminate excess handling and can resolve many possible genotypes/loci using a single non-fluorescent primer (p.1347, left col., ln.37).

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 103 as obvious in view of the teachings of the cited prior art. Applicants' arguments have been considered but are not found to be persuasive to withdrawn the rejection as set forth.

Applicants have argued (p.7-8 of the Remarks of 12/17/2008) that 'the present method of using only short, about 100bp fragments provides a surprising advantage that was not taught or suggested' by the prior art. Initially it is noted, as detailed previously discussed in the Advisory Action of 11/20/2008, that while ¶ [0077] of the specification teaches 'high efficiency amplification of very short amplicons (typically 100 bp)', the claims require only that primer pairs flank a nucleic acid region of about 100 bp long. Thus the claims require only primer pairs that can amplify an amplicon comprising about 100 bp, and do not in fact require a step of amplification of an amplicon that is 100 bp or less in length (i.e. the term 'flanks' requires only that the primer pairs surrounds the recited 'about 100 bp', and does not require an amplicon consisting of about 100 bp).

Applicants further argue, in support of the asserted unexpected result, that the prior art of Furlong et al (p.1194) teaches that the "relatively high percentage of wells apparently containing 0 sperm per well probably reflects failure of PCR in these wells,

as visual inspection of wells following flow-sorting estimated that >98% contained single sperm." However in the case of the data of Furlong et al, it is important recognize that the cited portion of the prior art indicates a 'relatively' high percentage of failure of PCR, where visual inspection indicates that >98% of samples had a single sperm cell. In this case, in comparing the teaching of the prior art to the data of the specification it is noted that the specification teaches (p.19, ¶ 76) that the estimated PCR efficiency of the claimed method is about 90-95%, but that value may in fact overestimate PCR efficiency. In the case of the prior art, Furlong et al appears to teach PCR efficiency of as high as 85.6% (Table 3, 'Efficiency:B') and the estimate of 'One Sperm' is 75.3%. Finally, with regard to the compared efficiency between the prior art and the instant disclosure, it is noted that the claims are drawn to methods of haplotyping, where the specification provides (Example, p.18-19) that in the analysis of a 3 SNP haplotype (¶72) the single reaction haplotyping efficiency (the ability to discern all three individual SNPs) is 40-45% (¶77). This disclosed haplotyping efficiency with 3 SNPs is in fact lower than the efficiency disclosed in Furlong et al (p. 1198, left col.) for the analysis of 4 markers:

> "Successful amplification of a single 96-well plate was as high as 93%, including 76% of wells which were informative (i.e., two or more loci were amplified) **and 47% in which all four loci amplified**." (emphasis added).

Thus the assertion that there is an unexpected result of increased genotyping efficiency with the method as claimed is not found to be persuasive and the rejection as set forth is **MAINTAINED**.

4. Claims 3, 9-11, 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruano et al (1990) (citation no. 30 on the IDS of 07/31/2006) in view of Furlong et al (1993) and Ross et al (citation no. 27 on the IDS of 07/31/2006) as applied to claims 1, 2, 4-8, 21 and 22 above, and further in view of Drysdale et al (2000) (citation no. 9 on the IDS of 07/31/2006).

The teachings of Ruano et al in view of Furlong et al and Ross et al are applied to claims 3, 9-11, 19 and 20 as they were previously applied to claims 1, 2, 4-8, 21 and 22.

Ruano et al in view of Furlong et al and Ross et al teaches a method for the determination of haplotypes amplified from a single DNA molecule and methods to obtain at least four genotype replicas, thus teaching all of the limitations of claims 1 and 2 (from which rejected claim 3 depends), as well as steps (a)-(d) of claim 9, and the limitations of claim 10, where the analysis of multiple deduced haplotypes to determine the haplotype of the subject is a statistical analysis.

Regarding the limitations of claim 11, Ruano et al teaches repetition of experimentation to resolve genotypes (p.6298 – right col., last paragraph), and further teaches that errors in haplotype determination should be held in check by analyzing replicate vials (p.6300, left col., lns.43-45).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the haplotype determination methods of Ruano et al in view of Furlong et al and Ross et al to produce and analyze 12-18

replicas. One would have been motivated to create multiple genotype replicas based on the assertion of Ruano et al that such methods increase the accuracy of the analysis (p.6298 – right col., last paragraph; p.6300, left col., lns.43-45). One of skill in the art would recognize that creating an increased number of replica genotypes would lead to further increased accuracy of haplotype determination, and the skilled artisan would be capable of creating, for example, 12 genotype analyses of single-molecule dilutions (e.g. Ruano et al teaches twelve such analyses in Fig 4).

Ruano et al in view of Furlong et al and Ross et al does not teach the comparison of a deduced haplotype with a haplotype from a control or a database of haplotypes from controls to determine association of the haplotype with a biological trait (as required by claim 3), or comparison of a deduced haplotype with known disease-associated haplotypes to indicate that the subject has, or is susceptible for, a disease (as required by step (e) of claim 9). Ruano et al in view of Furlong et al does not teach an anlysis comprising at least 5 or at least 10 primer pairs (claims 19 and 20).

Drysdale et al teaches the use of β_2-adrenergic (β_2AR) receptor haplotypes comprised of 13 polymorphic positions in the prediction of response to albuterol (p.10486, left col., lns.6-8), which is a biological trait.

Regarding claim 3 and step (e) of claim 9, Drysdale et al teaches a collection of (β_2AR) haplotype pairs found in a cohort of asthmatics (p.10486, right col., lns.3-10; Table 2) (thus a database of haplotypes), as well as the association of the five most common haplotype pairs with patient response to albuterol (Fig.3; p.10487, left col., lns.1-25). The reference further teaches comparing a haplotype to the database of

haplotypes and association data to determine association of the haplotype with a biological trait (Fig.3; p.10487, left col., lns.25-30).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to have compared haplotypes determined by the methods of Ruano et al in view of Furlong et al and Ross et al to a database of haplotypes as taught by Drysdale et al. One would have been motivated to perform a comparison of a haplotype determined by the methods of Ruano et al in view of Furlong et al and Ross et al with a haplotype from a control, or with known disease-associated haplotypes, based on the assertion of Drysdale et al that haplotypes are more predictive of phenotype, and that individual SNPs may have poor predictive power as pharmacogenetic loci (p.10488, right col., lns.13-17). With specific regard to claim 11, it would have been obvious to create and analyze numerous replicas in a comparison of a haplotype determined for a subject with known disease-associated haplotypes, including producing 12-18 replicas, to increase the accuracy of the analysis, as discussed earlier in this rejection. With specific regard to the requirements of claims 19 and 20, applying the teachings of Furlong et al (i.e. multiplex PCR using primer pairs for each polymorphic marker) to the analysis of Drysdale et al (i.e. analysis of haplotypes comprised of 13 polymorphic markers) would result in a method in which primer pairs flanking each polymorphic site are used to genotype the sample, which is a method in which at least 5 (claim 19) and at least 10 (claim 20) primer pairs are used each to amplify a different nucleic acid region.

5. Claims 12-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruano et al (1990) (citation no. 30 on the IDS of 07/31/2006) in view of Furlong et al (1993) and Ross et al (citation no. 27 on the IDS of 07/31/2006) as applied to claims 1, 2, 4-8, 21 and 22 above, and further in view of Rein et al (1998) (citation no.26 on the IDS of 07/31/2006) and Buckholz et al (1997).

The teachings of Ruano et al in view of Furlong et al and Ross et al are applied to claims 12-18 as they were previously applied to claims 1, 2, 4-8, 21 and 22.

Ruano et al in view of Furlong et al and Ross et al teaches a method for the determination of haplotypes amplified from a single DNA molecule and methods to obtain at least four genotype replicas, thus teaching the limitations of steps (b)-(e) of claim 12 and claim 13. Ruano et al teaches the limitations of steps (b)-(e) of claim 17 and methods to obtain at least four genotype replicas, as required by claim 18, where the analysis of multiple deduced haplotypes to determine the haplotype of the subject is a statistical analysis.

Regarding the limitations of claim 14 (requiring that 12-18 genotype replicas are produced), Ruano et al teaches repetition of experimentation to resolve genotypes (p.6298 – right col., last paragraph), and further teaches that errors in haplotype determination should be held in check by analyzing replicate vials (p.6300, left col., lns.43-45); although Ruano et al does not specifically teach producing 12-18 replica genotypes by repetition of the diluting, amplifying, genotyping steps.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the haplotype determination methods of

Ruano et al to produce and analyze 12-18 replicas, as required by claim 14. One would have been motivated to create multiple genotype replicas based on the assertion of Ruano et al that such methods increase the accuracy of the analysis (p.6298 – right col., last paragraph; p.6300, left col., lns.43-45). One of skill in the art would recognize that creating an increased number of replica genotypes would lead to further increased accuracy of haplotype determination, and the skilled artisan would be capable of creating, for example, 12 genotype analyses of single-molecule dilutions (e.g. Ruano et al teaches twelve such analyses in Fig 4).

Ruano et al in view of Furlong et al and Ross et al does not teach methods of comprising treating a sample with a composition that differentially affects an epigenetically modified nucleotide (step (a) of claim 12), or using bisulfite (claim 16) to modify a methylated nucleotide (claim 15), or digesting a nucleic acid sample with a methylation-sensitive restriction enzyme (step (a) of claim 17).

Rein et al teaches method for the identification of 5-metyhlcytosine and related modifications in DNA genomes (Table 1; p.2255, right col., first full paragraph).

Regarding claim 12, Rein et al teaches methods for analysis of 5-methylcytosine (m^5C, which is a modified nucleotide) by treating genomic DNA with a composition that differentially affects epigenetically modified nucleotides by converting non-methylated C to U, and not altering m^5C (p.2258 – Differential base modification by bisulfite), relevant to step (a) of claim 12. Rein et al thus teaches effectively creating polymorphisms (the content at a given nucleotide position can be a C if the position is methylated, or U

(which behaves similar to a T in subsequent base pairing processes) if the position is non-methylated) based on the epigenetic methylation modification (Fig 2).

Regarding claim 15, Rein et al teaches the analysis of 5-methylcytosine (m^5C), which is a methylated nucleotide (p.2258 – Differential base modification by bisulfite).

Regarding claim 16, Rein et al teaches the use of bisulfite for the treatment of a nucleic acid sample (p.2258 – Differential base modification by bisulfite; Table 1; p.2255, right col., ln.25).

Regarding claim 17, Rein et al teaches methods for analysis of methylated bases at specific DNA sites use modification-sensitive restriction endonucleases (Table 1; p.2257 - Modification-sensitive restriction endonucleases (MSREs); Fig 1). Relevant to step (a) of claim 17, the reference teaches the digestion of a sample with restriction enzymes that are sensitive to base modification (i.e. will not digest methylated sites) and restriction enzymes that require base modification (i.e. will only digest methylated sites) (p.2257, left col., lns.14-24; Fig 1). Relevant to step (e) of claim 17, Rein et al teaches the analysis of the methylation dependent digestion of a sample by Southern analysis and PCR amplification (Fig 1; p.2258, left col., lns.15).

Furthermore, the relevance of specific epigenetically modified methylation sites was known in the prior art at the time the invention was made. Buckholz et al teaches the analysis of several epigenetically modified methylation sites (e.g. p.118 - Table I) greater that are about one or more kilo base pairs apart in the analysis of genomic imprinting and Prader Willi syndrome.

It would have been prima facie obvious to one of skill in the art at the time the invention was made to have modified the haplotype determination methods of Ruano et al in view of Furlong et al and Ross et al so as to have included the methylation analysis methods of Rein et al and Buckholz et al. One would have been motivated to do so because Rein et al teaches that the status of methylation of any particular cytosine (i.e. 5-methylcytosine) in the genomes of eukaryotic cells plays a role in a variety of processes (p.2255, left col., first paragraph of introduction), where Buckholz et al provides specific loci and positions of relevant methylations. One would have been motivated to use the bisulfite treatment of Rein et al (relevant to claims 12-16) because Rein et al teaches that such methods are highly sensitive, are amenable to rapid genomic sequencing, and provide positive display of m^5C (Table 1). One would have been motivated to use the MSRE method of Rein et al (relevant to claim 17 and 18) because Rein et al teaches that such methods provide a rapid analysis of large DNA regions, and are highly sensitive. With particular regard to step (e) of claim 17, the combination of the restriction enzyme digestion methods of Rein et al (as summarized in Fig 1 of Rein et al) and the haplotype determination methods of Ruano et al would create a method where, for example, the DNA sample amplified by GR1, GR2, GR3, and GR4 (as from the nomenclature of Ruano et al) would be produce by restriction digestion (as taught in Fig 1 of Rein et al) instead of by a first PCR amplification with GR5 and GR6 (as taught by Fig 1 of Ruano et al). Thus the determined haplotype would include polymorphic markers such as SNPs (determined by PCR as taught by Ruano et al) that are next to (e.g. the polymorphic sites would be adjacent to the cut site

determined by the action of an m^5C-requiring restriction enzyme) the methylation site analyzed by the restriction enzyme.

6. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ruano et al (1990) (citation no. 30 on the IDS of 07/31/2006) in view of Furlong et al (1993) and Ross et al (citation no. 27 on the IDS of 07/31/2006) as applied to claims 1, 2, 4-8, 21 and 22 above, and further in view of Gerhard et al (1984).

The teachings of Ruano et al in view of Furlong et al and Ross et al are applied to claim 23 as they were previously applied to claims 1, 2, 4-8, 21 and 22.

Ruano et al in view of Furlong et al and Ross et al does not specifically provide for one polymorphic site in a first nucleic acid region that is 15-20 kilo base pairs apart from a polymorphic site in a second nucleic acid region.

However, at the time the invention was made haplotypes comprising polymorphic positions that are 15-20 kilo base pairs apart were well known in the art. Gerhard et al teaches a B-globin haplotype including polymorphic positions that are 15-20 kilo base pairs apart (Fig 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of Ruano et al in view of Furlong et al and Ross et al to analyze a haplotype comprising of markers in the B-globin cluster as taught by Gerhard et al. One would have been motivated to analyze the markers of Gerhard et al based on the teachings of Gerhard et al that such analyses

may provide insight into the distribution if and mechanics underlying meiotic crossing over.

Withdrawn Double Patenting

7. The provisional rejection of claims under Double Patenting over the claims of conflicting application 10/759,519, as set forth in the previous Office Action is **WITHDRAWN** in light of the amendments to the claims of the instant application.

Conclusion

8. No claim is allowable. No claim is free of the teachings of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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/Stephen Kapushoc/